(12) UK Patent Application (19) GB (11) 2 107 191 A

(21) Application No 8220968
(22) Date of filing 20 Jul 1982
(30) Priority data
(31) 289082
310047
312491
325206
(32) 31 Jul 1981
9 Oct 1981
19 Oct 1981
27 Nov 1981
(33) United States of America (US)
(43) Application published 27 Apr 1983
(51) INT CL³ A61M 5/14
(52) Domestic classification A5R CH
(56) Documents cited GBA 2059776
GB 1586645
GB 1537718
EP 0005606
(58) Field of search A5R
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(54) **Parenteral delivery system**

(57) In a parenteral delivery system comprising a fluid container (11) attached to a conduit (20) including a drip chamber 18, a formulation chamber (25) containing a formulation to be added to the fluid supply debouches into the conduit downstream of the drip chamber.

FIG. 1

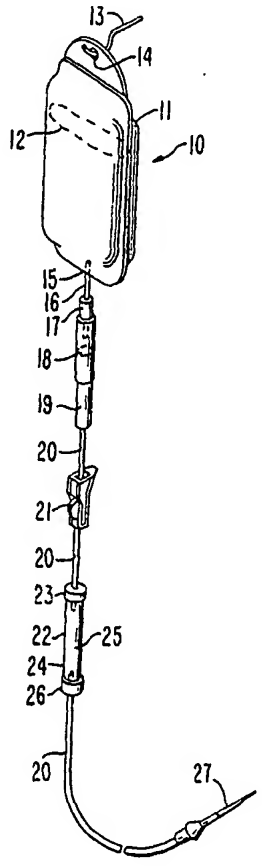

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FIG. 1

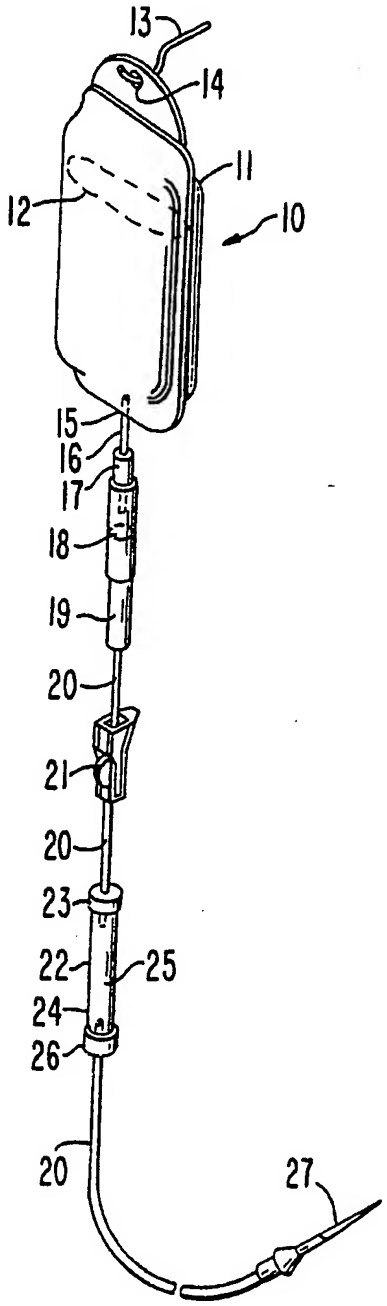

FIG. 2

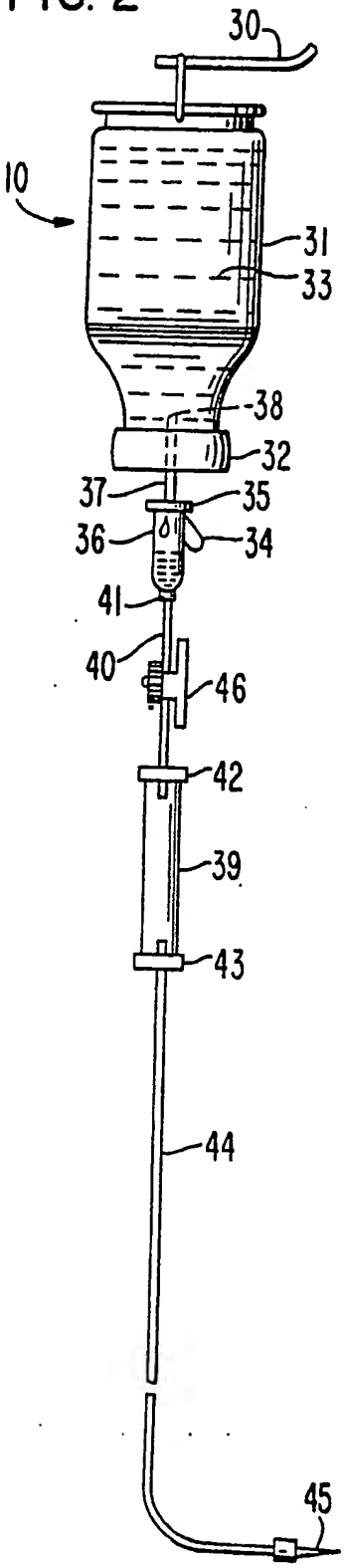

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FIG. 3

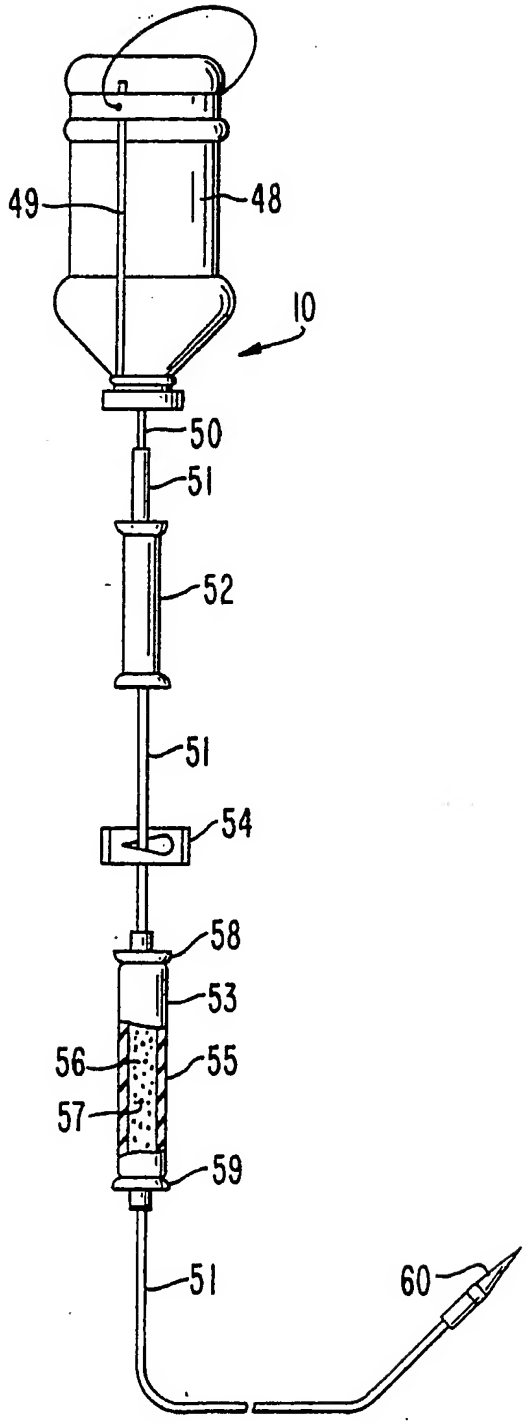

FIG. 4

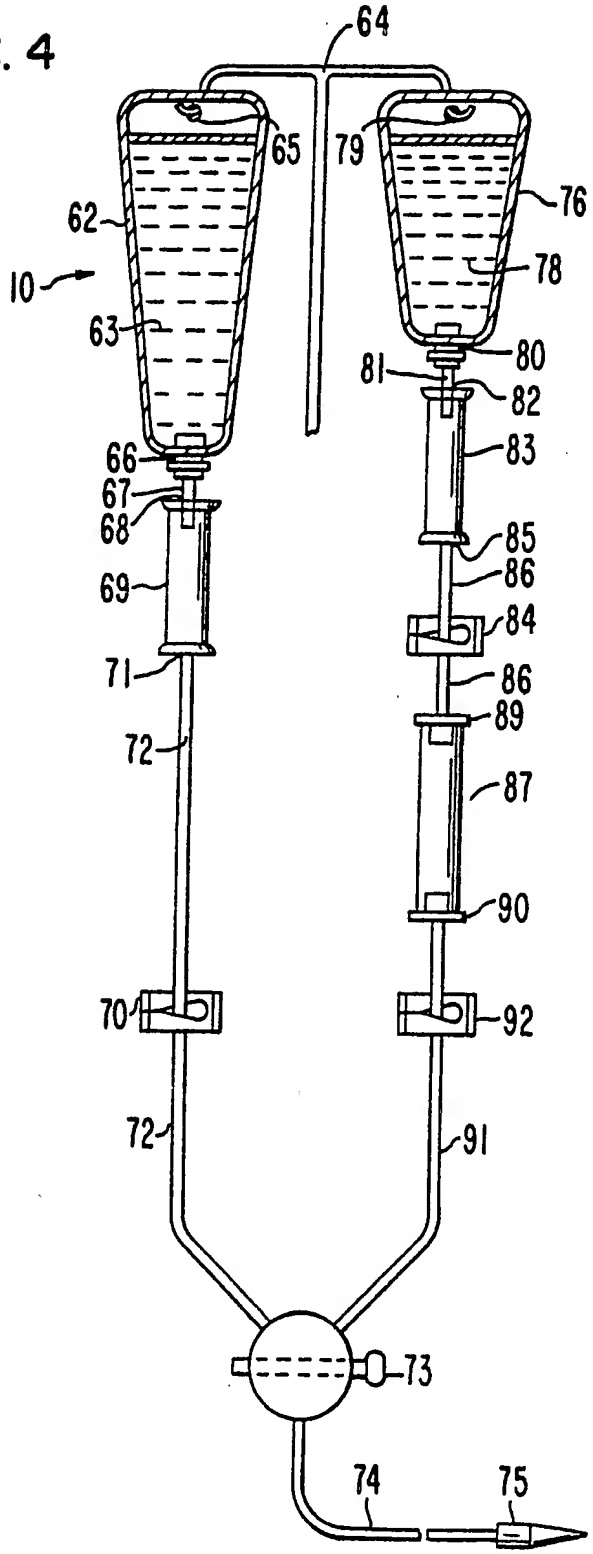
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FIG. 5

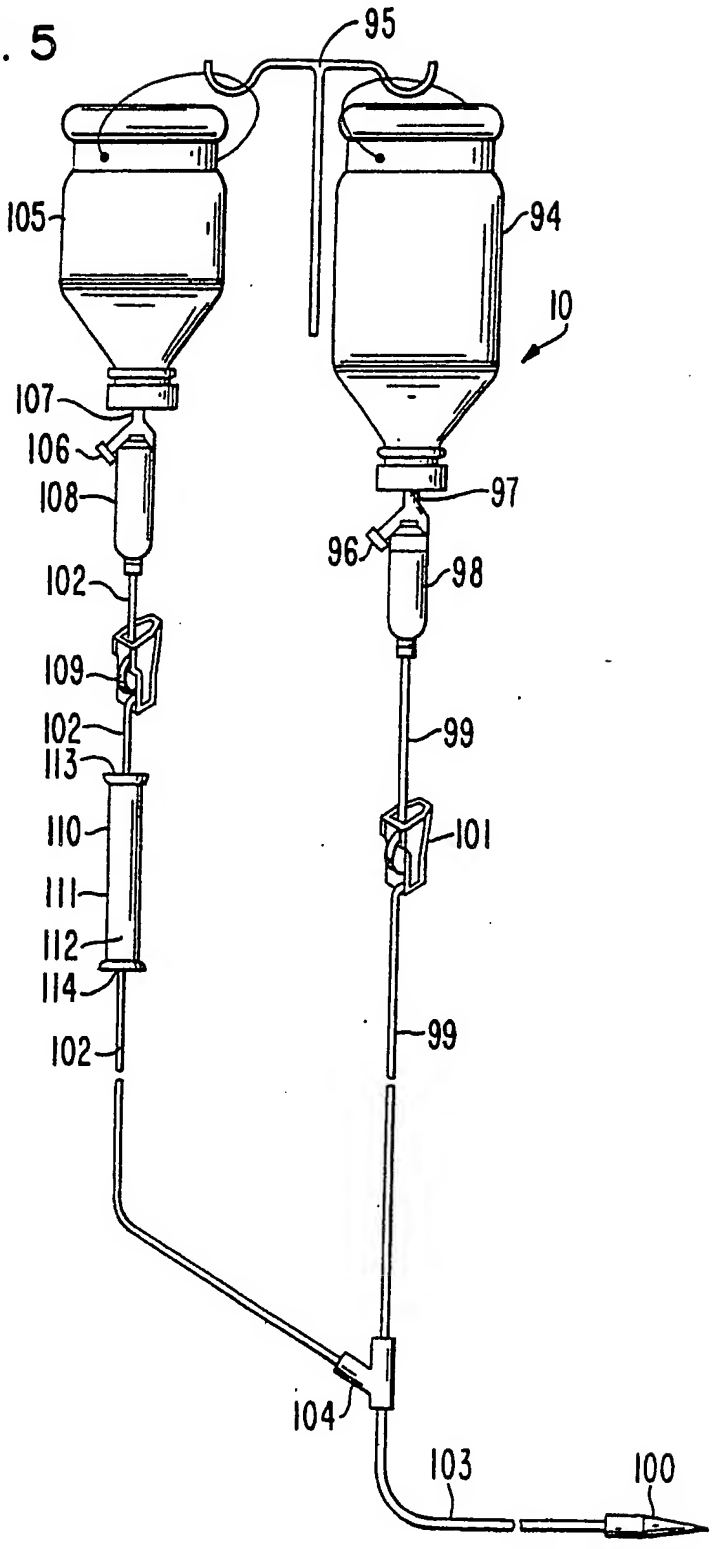
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FIG. 6

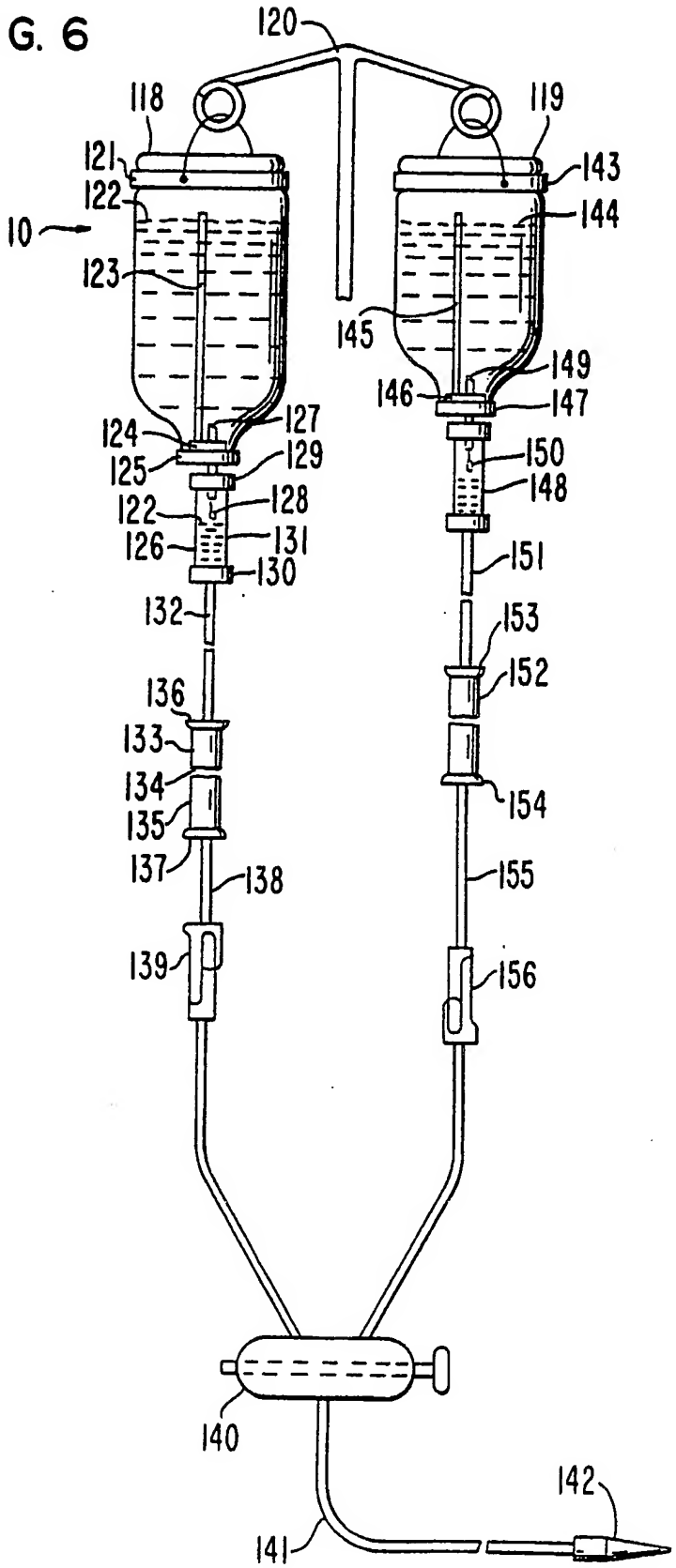
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FIG. 7

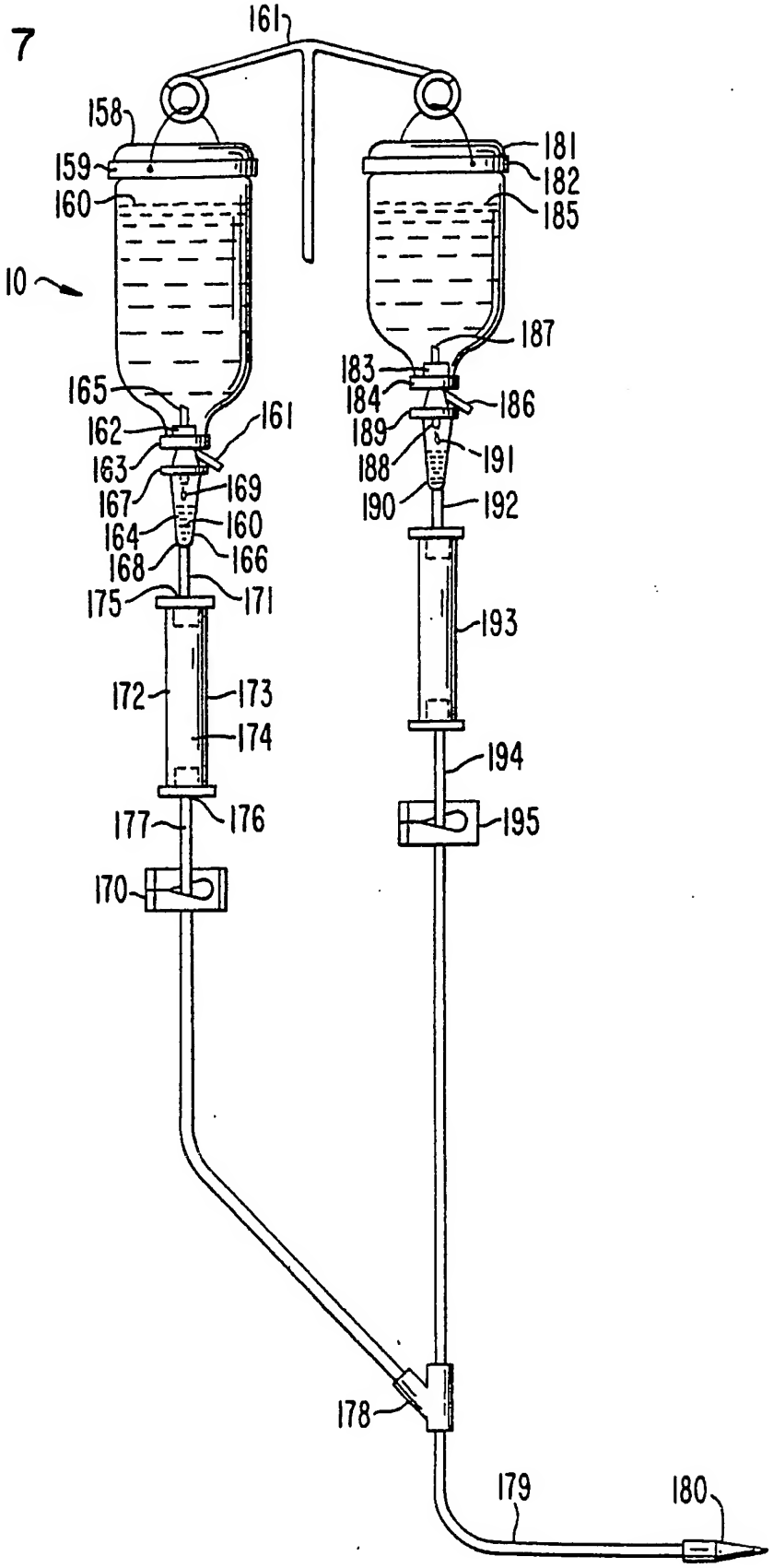
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FIG. 8

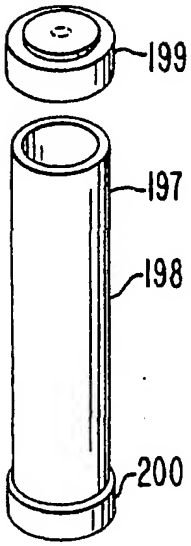


FIG. 9

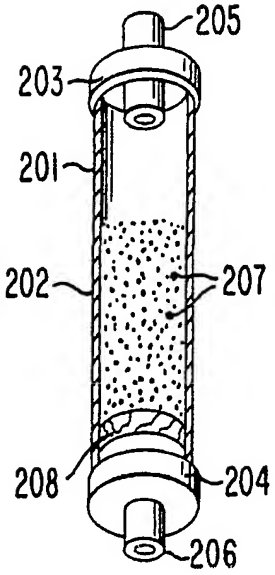


FIG. 10

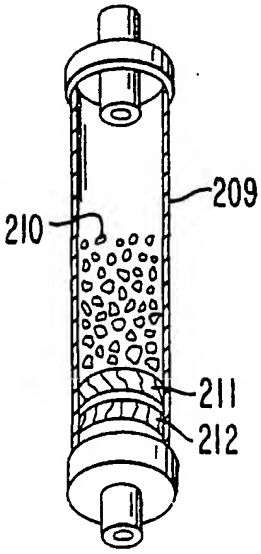


FIG. 11

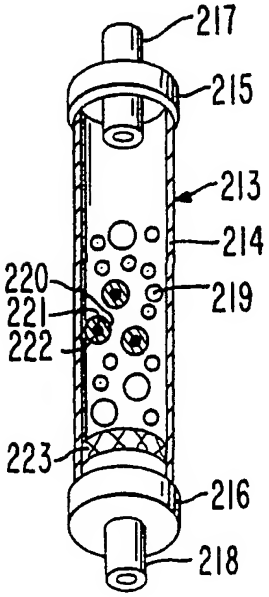


FIG. 12

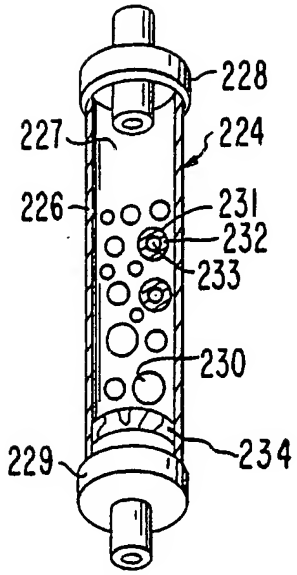


FIG. 13

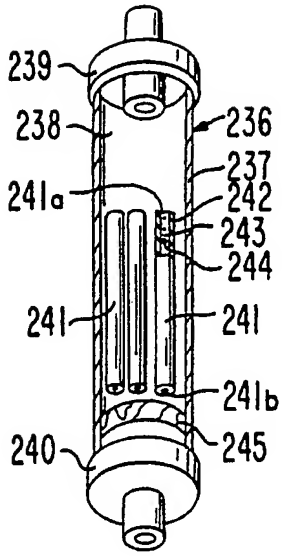


FIG. 14

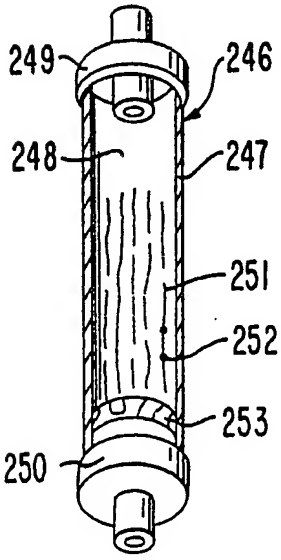


FIG. 15

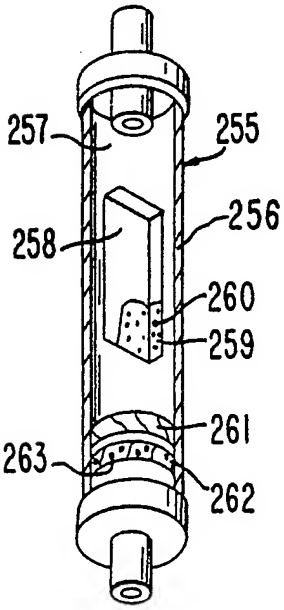


FIG. 16

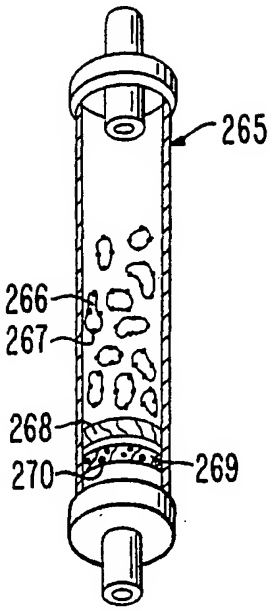


FIG. 17

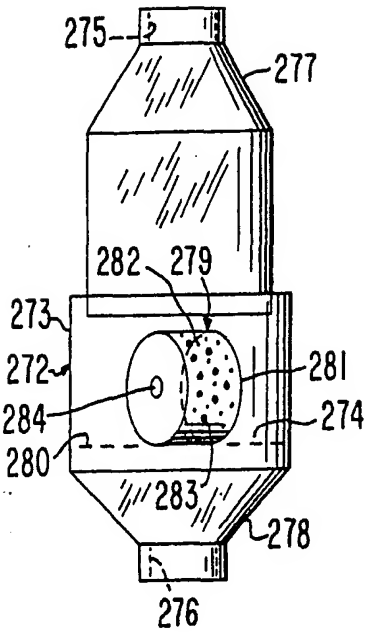


FIG. 18

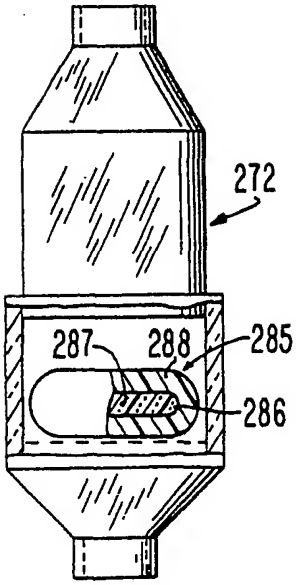


FIG. 19

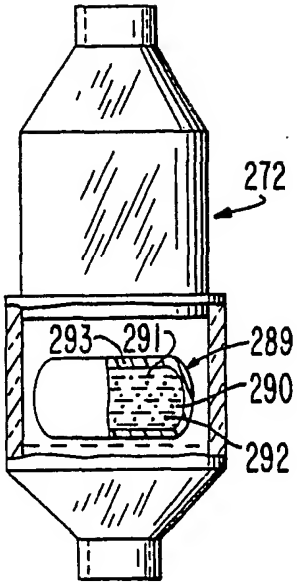


FIG. 20

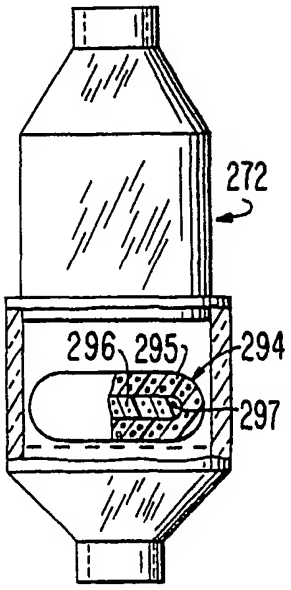


FIG. 21

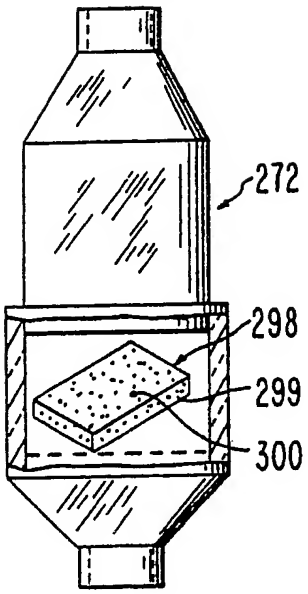


FIG. 22

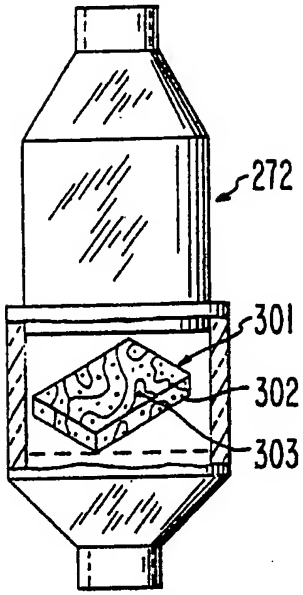


FIG. 23

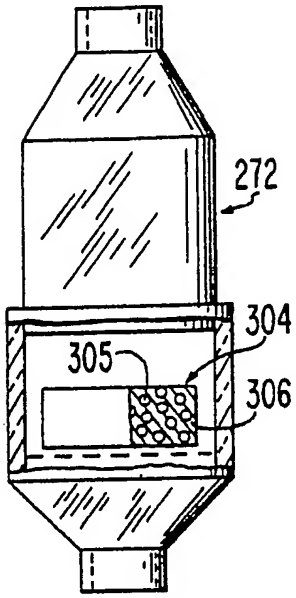


FIG. 24

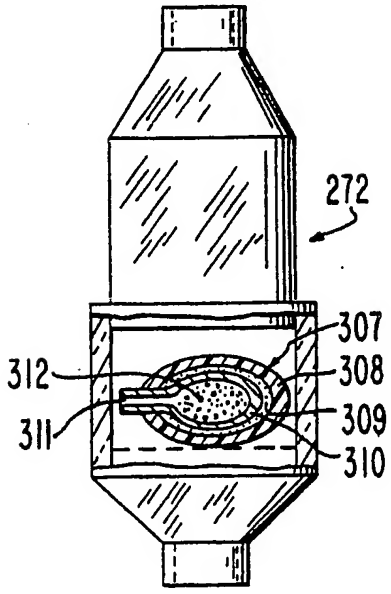
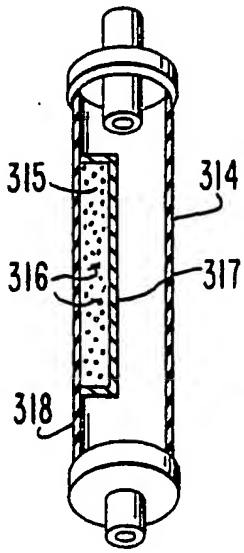


FIG. 25



SPECIFICATION

System for parenteral delivery of a beneficial agent

This invention pertains to both a parenteral delivery system and to a formulation chamber containing a beneficial agent. The invention also relates to a method of administering parenterally a beneficial agent using the parenteral delivery system comprising the agent formulation chamber, and to a method for adding an agent to a fluid.

The parenteral administration of medical liquids is an established clinical practice. The liquids are administered generally intravenously, and the practice is used extensively as an integral part of the daily treatment of medical and surgical patients. The liquids commonly administered include blood, blood substitutes, dextrose solution, electrolyte solution, and saline. Generally, the liquids are administered from an intravenous delivery system having a container suspended above the patient, with the liquid flowing through a catheter hypodermic needle set to the patient.

The administration of liquids intravenously is a valuable and important component in the treatment and care of the patient; however, it does not provide a satisfactory means and method for administering concomitantly therewith a beneficial agent. Hitherto, a beneficial agent is administered intravenously by

(1) temporarily removing the intravenous system and halting the flow is liquid, and then intravenously administering the agent to the patient followed by reinserting the intravenous system into the patient;

(2) adding the agent to the liquid in the container and then carried by the flow of the liquid to the patient;

(3) adding the agent to a liquid in a separate container called a partial fill that is connected to the primary intravenous line through which line the agent is carried by the flow of liquid to the patient;

(4) an agent is contained in a piggyback vial into which is introduced an intravenous fluid, with the vial subsequently connected to the primary line through which the drug is administered to the patient; or

(5) administering the agent by a pump that exerts a force on a liquid containing agent for intravenously administering the liquid containing the agent.

These techniques have major disadvantages, for example, the administration of an agent through repeated insertion of a needle leads to unnecessary pain and trauma, they require separate connections for joining the primary intravenous line which further complicates intravenous administration, while the use of pumps can produce pressure that can vary at the delivery site and the pressure can give rise to thrombosis, the rate of agent delivery to the patient often is unknown as it is not rate-controlled agent delivery but dependent on the flow of fluid. Furthermore they require preformulation of the agent medication by the hospital pharmacist or nurse.

Accordingly, a principal object of this invention is to provide a parenteral delivery system for administering a beneficial agent at a controlled rate and in an improved manner for optimizing the care of a patient whose prognosis benefits from intravenous delivery of a beneficial agent.

According to the present invention, there is provided a parenteral delivery system comprising a container for a pharmaceutically acceptable fluid means for introducing fluid from said container to a patient, conduit means connecting said container and said introduction means, said conduit means including a drip chamber for determining the rate of fluid flow within said conduit means, and a formulation chamber disposed to debouch into said conduit means downstream of said drip chamber and adapted to contain a pharmaceutically acceptable formulation capable of forming a fluid agent formulation with said fluid for supply thereof to the patient.

The invention seeks to provide therefore a parenteral delivery system comprising a formulation chamber containing a beneficial agent or formulation for admitting the agent into a parenteral fluid for optimizing the care of a patient or parenteral therapy.

The formulation chamber may contain a unit dosage said formulation and the chamber may be adapted for use in a parenteral delivery system for ministering the formulation at a controlled rate by the dosage form into a parenteral fluid admitted into the chamber.

The formulation chamber accommodating a beneficial agent or formulation may have a rate controlling membrane for delivering the formulation at a rate governed by the rate controlling membrane into the pharmaceutically acceptable fluid.

In one aspect of the invention there is provided a parenteral delivery system comprising an agent formulation chamber containing a dosage form of a formulation for administering at a controlled rate the said formulation into parenteral fluid admitted into the chamber.

The formulation chamber may house an agent delivery device for admitting an agent or formulation at a rate essentially controlled by the device into a parenteral fluid admitted into the chamber.

In a further embodiment of the invention there is provided a parenteral delivery system comprising (1) a primary fluid path, and (2) a secondary fluid path comprising a formulation chamber containing (a) an agent delivery device for delivering an agent into a medical fluid that flows into the chamber, or (b) a beneficial agent, which agent in either instance forms in situ an agent solution for administration to a patient.

The parenteral delivery system of the invention may include (1) a primary fluid path comprising a formulation chamber containing (a) an agent delivery device for delivering an agent into a

medical fluid that flows into the chamber, or (b) a beneficial agent; and (2) a secondary fluid path comprising a formulation chamber containing (a) an agent delivery device for delivering an agent into a medical fluid that flows into the chamber, or (b) a beneficial agent, which agent in either (a) or (b) forms in situ an agent solution for administering to an animal or human.

In another aspect, the invention relates to a parenteral delivery system and an agent formulation chamber, which formulation chamber is adapted for use with the parenteral system. The formulation chamber contains (a) a beneficial agent that is self-formulating or self-mixing with a parenteral fluid entering the formulation chamber in situ and then infused into a biological recipient, or the formulation chamber contains (b) a beneficial agent wherein the agent is originally present in an agent delivery means such as an agent delivery device, or a rate controlled dosage form housed in the chamber, which stores an amount of a beneficial agent for executing a prescribed program and provide for a preprogrammed, unattended delivery of agent into fluid that enters into the formulation chamber. The beneficial agent on its release by the delivery means is formulated in situ with parenteral fluid that enters into the formulation chamber. The delivery means in one presently preferred embodiment releases beneficial agent at a controlled rate that is essentially independent of the volume rate of parenteral fluid entering the formulation chamber, and then infused into a recipient. The invention also includes a parenteral delivery system for administering a fluid agent formulation, wherein the agent is formulated in situ with fluid and wherein the parenteral delivery system comprises in combination: (a) a container for storing a pharmaceutically acceptable fluid which is also a pharmaceutically acceptable carrier for the agent; (b) a formulation chamber comprising a wall surrounding a lumen and having a surface inlet that permits communication with the container to let fluid flow from the container into the formulation chamber, and an outlet surface through which agent formulation exits the chamber; (c) a beneficial agent, a dosage form, or a delivery device in the formulation chamber; and (d) a conduit that communicates with the chamber outlet and extends to a patient recipient site.

In a further embodiment a parenteral delivery system may comprise (1) a primary fluid path consisting of a container of a medical fluid and a primary tube that communicates from the container to a common tube that leads to an infusion site in the animal; and (2) a secondary fluid path consisting of a minicontainer of a medical fluid in fluid communication with an agent formulation chamber that communicates with a secondary tube and then with the common fluid path for infusion into the animal.

Another embodiment of the invention concerns the parenteral delivery system comprising: (1) a primary fluid path consisting of a container of a medical fluid, a drip chamber, an agent formulation chamber, and a primary tube that communicates with the formulation chamber and a common tube that leads to an infusion site in an animal; and (2) a secondary fluid path consisting of a container of a medical fluid, a drip chamber, an agent formulation chamber, and a secondary tube that communicates with the formulation chamber and the common tube that leads to an infusion site.

Following is a description by way of example only and with reference to the accompanying drawings of methods of carrying the invention into effect.

In the drawings:—

Figure 1 is a perspective of an intravenous delivery system in accordance with the invention.

Figures 2 and 3 are side views of further embodiments of the present invention.

Figures 4, 5, 6 and 7 are side views partly in section of embodiments of the delivery system of the invention having more than one container for medical fluids.

Figures 8 to 25 are details of formulation chambers that may be used in the systems in accordance with the invention.

Figure 1 illustrates an operative intravenous delivery system provided by the invention and it is generally designated by the numeral 10. System 10 comprises a container 11 formed of a flexible, or a semi-rigid, preferably transparent plastic, such as polyvinylchloride, or a polyolefin, and it contains a medical fluid 12 adapted for intravenous administration. Medical fluid 12 in container 11 will typically be a sterile solution, such as an aqueous solution of dextrose, a solution of dextrose in saline, an electrolyte solution and saline. Medical fluid 12 also is a pharmaceutical vehicle or carrier for intravenous administration, and it is a pharmaceutical carrier for a beneficial agent that is to be administered to a recipient. Container 11, in the embodiment illustrated, is non-vented, the medical fluid in it is at atmospheric pressure, and the container collapses as it empties of fluid 12. Container 11 usually is adapted to be hung neck-down from a hanger 13 by a bib or hole 14 that connects or is integrally formed as part of container 11. Container 11, at its end distant from its hanging end, that is, at its neck end has an administration port 15 adapted for receiving an administrative set.

The administration set provided by this invention is used to deliver fluid 12 and a beneficial agent admitted into intravenous delivery system 10 to a patient. The administration set is sterile, pyrogen-free and disposable. The administration set comprises the components described hereafter, and it connects with port 15 of container 11. Port 15 can be a diaphragm in container 11, not shown, or port 15 can be a hollow connector 16. Connector 16 is adapted to receive end 17 of drip chamber 18, which end 17 fits snugly over connector 16. Drip chamber 18 is used to trap air and permit adjustment of the rate of flow of fluid 12 from container 11 as the flow

proceeds drop wise. An outlet 19 of drip chamber 18 is connected to a first segment of tubing 20 that fits into outlet 19. An adjustable clamp 21 of the roller or screw tube on tubing 20 pinches the internal diameter of tubing 20 to regulate flow in cooperation with drip sight chamber 18. A second segment of tubing 20 connects to inlet 23 of agent formulation chamber 22. A third segment of tubing 20 connects to outlet 26 of formulation chamber 22 and to an adapter-needle assembly 27 that is inserted into a vein and sometimes an artery of a warm-blooded animal.

Agent formulation chamber 22 is a unique component of the intravenous delivery system both as the chamber alone and in combination with the system. Formulation chamber 22 is sized and adapted for use in intravenous systems, it is self-contained, self-priming, self-powered, self-formulating, and amenable to low cost manufacturing. Formulation chamber 22 contains an intravenously administrable beneficial agent, and the use of formulation chamber 22 with agent therein does not require any reconstitution or admixture prior to use. Agent formulation chamber 22 is a lightweight disposable chamber comprising a wall 24 that surrounds and defines an internal space or lumen 25. Chamber 22 has an inlet 23 adapted and sized for placing chamber 22 into an intravenous delivery system, and it has an outlet 26 also adapted for placing the chamber in the system. Inlet 23 and outlet 26 are made for receiving tube 20. Chamber 22 is made of glass, plastic or the like, and as illustrated it is made of a transparent material for illustrating its structure and an agent housed therein. The agent in chamber 22 can be in any pharmaceutical state that forms an agent formulation with the fluid that enters the chamber. Exemplary pharmaceutically acceptable forms include solid, crystalline, microcrystalline, particle, pellet, granule, powder, tablet, spray-dried, lypohilized, compressed forms that undergo disintegration and dissolution in the presence of parenteral fluid including intravenous fluid such as compressed particles, compressed powders, compressed granules, friable layers of agent, in a delivery device that releases the agent at a rate controlled by the device into fluid that enters formulation chamber 22, in a dosage, and the like. Agent formulation chamber 22 generally will store an amount of beneficial agent in a delivery device, a dosage form, in a pharmaceutical form, the like, for executing a prescribed therapeutic or beneficial program. That is, an amount of agent for a preprogrammed, unattended delivery of a therapeutically or a beneficially effective amount of the agent to produce a therapeutic or a beneficial result. Agent formulation chamber 22 generally will have a capacity of from about 10 milliliters to 250 milliliters of fluid or more, and it can house from about 5 milligrams to 20 grams of agent or more in the various pharmaceutical forms and delivery devices.

The expression beneficial agent, as used herein, generically denotes any substance that produces a therapeutic or a beneficial result, such as a drug, a carbohydrate, an electrolyte and/or the like. The term fluid or liquid denotes a fluid or liquid that can be administered parenterally including intravenously, comprising pharmaceutically acceptable fluids that are also a pharmaceutically acceptable carrier for an agent, such as water, isotonic saline, Ringer's lactate, and the like. The term formulation, and agent formulation as presently used herein, generically indicates the beneficial agent is formulated, mixed, added, dissolved, suspended, carried, and/or the like in or by the fluid in a physical-chemical form acceptable for parenteral including intravenous administration. In an additional embodiment of the invention, formulation chamber 22 can simultaneously act as a drip chamber while housing a device or an agent. In this embodiment, the formulation chamber-drip chamber is used to achieve a desired fluid drop rate. For example, the formulation chamber-drip chamber can have a fast drop rate for adults, or it can have a slower drop rate for pediatric use. The formulation chamber-drip chamber can be made with various sized inlets for controlling the rate of drip, or the drip can be controlled by a regulating clamp on the tubing conveying fluid thereto. The formulation chamber-drip chamber can deliver, for example from 2 to 75 drops per milliliter over from 1 minute to 1 hour. More preferably, the therapist can adjust the rate of flow of 1 to 20 drops per minute, or for the need of the patient. An additional disclosure pertaining to formulation chamber 22 is presented later in this specification.

Figure 22 illustrates another operative parenteral therapeutic system generally designated 10 as provided by the invention. System 10 is supported in delivery position by support 30. System 10 is a vented-type system that requires air to operate. System 10 comprises a container 31 made of glass or rigid clear plastic suitably sealed with a rubber stopper, not shown, that is held in container 31 by annular closure rim 32. Container 31 contains a fluid 33 designated preferably for intravenous administration. Air enters system 10 through air inlet 34 formed as part of the inlet closure 35 of drip chamber 36. A spike 37 that is hollow pierces the rubber closure of container 31 and it serves as a conduit for letting air travel from air inlet 34 into container 31 and as a conduit for letting fluid 33 travel from container 31 into drip chamber 36. One point 38 of spike 37 is seen in container 31, the other point of spike 32, not seen, enters drip chamber 36 for conveying fluid 33 from container 31 to drip chamber 36. Drip chamber 36 is of conventional, hollow, tubular-like design consisting of a wall surrounding an internal fluid receiving lumen and it is connected to an agent formulation chamber 39 through a first section of tube 40 inserted into its outlet end 41 of drip chamber 36, and it also is inserted into formulation chamber end 42 adapted for receiving tube 40. The other end 42 of formulation chamber 39 is adapted for receiving a second section of

tube 44. Formulation chamber 39 is made of glass or plastic, and it is preferably transparent. Formulation chamber 39 can have any shape adapted for use in a parenteral delivery system including intravenous delivery systems, and it is preferably round and its length exceeds its width. Ends 42 and 43 fit snugly over the wall of chamber 39 to form an air-tight, leak-proof closure for housing a delivery system that releases an agent for forming an agent solution in situ, in chamber 39 with fluid 33 entering chamber 39 from container 31 by mixing or dissolving therein. Tubing 44 conveys solution containing beneficial agent from chamber 39 to needle 45 for administration to a hose. A regulating clamp 46 is provided on tube 40 for pinching the internal diameter of tube 40 for regulating the flow of fluid 33 through the system 10.

Figure 3 illustrates another parenteral mainly intravenous system 10 provided by the invention. System 10 comprises in combination a container 48 that is a reservoir of a pharmaceutically acceptable fluid and it has an internal venting tube 49 which allows air to enter the container as medical fluid is infused into a patient. Container 48 is closed with a stopper, now shown, and it has a hole for venting tube 49. Container 48 is connected through a non-vented hollow spike adaptor 50 to a parenteral system for sending medical fluid from container 48 through system 10 to a patient. Spike 50 connects to a first section of tubing 51 that enters into a drip chamber 52. Drip chamber 52 is, as previously described, made preferably of a see through material such as glass or a plastic for visibly counting a measurable number of drops that pass through said chamber over unit time. A second section of tubing unites drip chamber 52 with a formulation chamber 53. The second section of tubing 51 passes through a clamp 54 used for regulating flow. Formulation chamber 53 comprises a wall 55 that surrounds an internal space 56. Chamber 55 houses in space 56 a dosage unit amount of agent 57, as represented by dots, for performing a beneficial program, or it can house a delivery device, or other pharmaceutical form. Agent 57 is present in a pharmaceutically acceptable form that can undergo dissolution, or it can disintegrate into smaller parts and dissolve in the presence of liquid in chamber 55 to form an agent solution. The chamber 55 can optionally contain a filtering element for providing a sterile fluid by removing particulate matter and/or bacteria from the fluid, which element does not interfere with the rate of fluid passing through the chamber. Delivery from such system can be controlled, for example, by the rate of dissolution as governed by particle size of agent and the solubility of the agent in the fluid, by the rate of release by a delivery device, and the like. Chamber 55 has an end 58 for receiving incoming tube 51 and medical fluid from container 48, and it has an end 59 for receiving outgoing tube 51. Tube 51 carries the agent solution from chamber 53 comprising a beneficially effective amount of agent 57 through needle 60 to a patient for producing the intended beneficial effect.

Figure 4 represents a parenteral delivery system provided by the invention and designated by the numeral 10. System 10 comprises a primary container 62 formed of a flexible, or a semi-rigid preferably transparent plastic, such as a non-toxic polyolefin, polyvinyl chloride or the like. Primary container 62 is a large volume parenteral, LVP, container and it contains a medical fluid 63 adapted for parenteral, intravenous or other therapy. Medical liquid 63 in container 62 will be typically a sterile solution, such as an aqueous solution of dextrose, electrolytes, or saline. Container 62, in the embodiment illustrated, is non-vented, the medical fluid is at atmospheric pressure, and the container collapses as it empties of medical fluid 63. Container 62 usually is adapted to be hung neck-down from a hanger 64 by a bib or hole 65 that connects, or is integrally formed as part of container 62. Container 62, at its end distant from its hanging end, that is, at its neck end, has an administration port adapted for receiving a primary fluid path.

The primary path is used to deliver medical fluid 62 by parenteral therapeutic system 10 to a patient. The primary path is sterile, pyrogen-free, and disposable. The primary path comprises the components described hereinafter, and it connects with port 66 of container 62. Port 66 can be a diaphragm in container 62, not shown, or port 66 can be an adapter for receiving a hollow connector 67. Connector 67 is made to receive end 68 of drip chamber 69. Drip chamber 69 is used to trap air and it also permits, in cooperation with regulator clamp 70, adjustment of the rate of flow of medical fluid 63 from container 62 as the flow proceeds dropwise. An outlet 71 of drip chamber 69 is connected to one end of a primary tube 72 that passes through regulator clamp 70 for pinching its internal diameter to regulate flow in cooperation with drip sight chamber 69. The other end of primary tube 72 connects to a valve 73, beyond which common tube 74 connects from valve 73 to an adapter needle assembly 75 that is inserted, for example, into the vein of a warm-blooded animal.

System 10 further comprises a secondary fluid path, which secondary path consists of a secondary container 76 or minibag formed of a flexible, or a semi-rigid preferably transparent plastic, such as a non-toxic polyolefin, polyvinyl chloride or the like. Secondary container 76 is a small volume parenteral, SVP, container and it contains a medical fluid 78 adapted for parenteral, intravenous or other therapy. Medical fluid 78 is a pharmaceutical vehicle for parenteral administration, that is, it is a pharmaceutical carrier for a drug that is to be administered to a recipient. Container 76, in the embodiment illustrated, is non-vented, medical fluid 78 is an atmospheric pressure, and the container collapses as it empties of medical fluid 78. Container 76 is adapted to be hung neck-down from a hanger 64

by a bib or hole 79 that connects, or is integrally formed as a part of container 76. Container 76, at its end distant from its hanging end, that is, at its neck end; has an administration port adapted for receiving a secondary fluid path.

The secondary fluid path provided by the invention is used to deliver medical fluid 78 to which a drug is added to a patient. The secondary path is sterile, pyrogen-free and disposable. The secondary path comprises the components described hereinafter, and it connects with port 80 of container 76.

Port 80 can be a diaphragm in container 76, not shown, or port 80 can be an adapter for receiving a hollow connector 81. Connector 81 is made to receive end 82 of drip chamber 83. Drip chamber 83 is used to trap air and it also permits, in cooperation with regulator clamp 84, adjustment of the rate of flow of medical fluid 78 from container 76 as the flow proceeds dropwise. An outlet 85 of drip chamber 83 is connected to one end of a segment of secondary tube 86 passing through regulator clamp 84 for pinching its internal diameter to regulate flow in cooperation with sight drip chamber 83. The other end of secondary tube 86 connects to an agent formulation chamber 87. Regulator clamp 84 is used for governing the flow of fluid into an agent formulation chamber 87. Formulation chamber 87 is made of glass or plastic, and it is preferably transparent. Formulation chamber 87 can have any shape adapted for use in a parenteral therapeutic system, and it is preferably round and its length exceeds its width. The end of secondary tube 86 mates snugly with end cap 89 of chamber 87. The end of the secondary tube can fit into cap 89 or it can slide over a tube receiving member of cap 89 to form an air-tight, leak-proof chamber for containing at least one beneficial agent, or a delivery device. Chamber 87 optionally is equipped with a release rate controlling membrane, not shown, for example a microporous membrane or the like, that governs the rate of release of agent solution from chamber 87. A release rate controlling membrane can rest on a sintered glass support integrally made into a chamber, optionally a membrane can be sealed adhesively to the inside wall of chamber 87, fused thereto, be supported by the wall of the chamber pinched inwardly, rest on a rim in the chamber, or it can be supported or suitably fixed to end cap 90 positioned in chamber 87. A segment of secondary tube 91 conveys agent solution from chamber 87 to valve 73. A regulator clamp 92 is provided optionally on tube 91 as an aid in governing the flow of agent solution from the formulation chamber. Regulator clamps 91 can be used alone, in cooperation with clamp 84, in cooperation with valve 73, and both in cooperation with valve 73 for governing fluid flow and agent solution flow through the secondary path. Valve 73, in a presently preferred embodiment, is a three position valve. Agent solution is conveyed from valve 73 through common tube 74 to needle assembly 75 for administration to a recipient. That is, fluid can be conveyed from the primary path, from the secondary path, or from both paths by setting the valve for flow to a recipient. For example, fluid can be conveyed through tube 72 valve 73, tube 74 and needle 75, or from tube 91, valve 73, tube 74 and needle 75, or the valve can be set for conveying fluid from both paths.

Figure 5 represents a parenteral delivery system provided by the invention and designated by the numeral 10. System 10 of Figure 5 illustrates a vented-type system that requires air to operate. System 10 comprises a glass container 94, suitably sealed with a rubber stopper and it contains a medical fluid acceptable for parenteral including intravenous administration. Container 94 is supported in delivery position by support 95, and air enters container 94 via air filter 96 connected to container 94 through spike 97 that is hollow and pierces the rubber closure of container 94. The other point of spike 97, not seen, enters a drip chamber 98 and it conveys medical fluid from container 94 into drip chamber 98. Drip chamber 98 is connected to a primary fluid path 99 formed of a medical grade tubing that conveys medical fluid to needle 100. A roller valve clamp 101 is provided on fluid path 99 for restricting the internal diameter of primary path 99 for regulating the flow of fluid through primary path 99. System 10 of Figure 5 also comprises a secondary fluid path 102 that joins a common path 103 at branch coupler 104. Branch coupler 104 can be made as a Y-type connecting tube for receiving primary path 99, secondary path 102 and common path 103.

The secondary path comprises a container 105 that is a mini-container or a minibottle formed of glass, and suitably sealed with a rubber stopper, not visible, and it contains a medical fluid acceptable for parenteral including intravenous administration. Container 105 is supported in delivery position by support 95, and air enters container 105 through a filter 106 connected to container 105 through spike 107, which spike is hollow and pierces the rubber closure of container 105. The other point of spike 97, not seen, enters a drip chamber 108 and it conveys medical fluid from container 105 into drip chamber 108. Drip chamber 108 is connected to a secondary fluid path 102 formed of a medical grade tubing that conveys medical fluid transporting a beneficial agent to needle 100. A roller valve clamp 109 is provided on secondary fluid path 102 for restricting the internal diameter of secondary path 102 for regulating the flow of fluid through the secondary path into agent formulation chamber 110. Agent formulation chamber 110 is sized and adapted for use in parenteral delivery system 10. Agent formulation chamber 110 is self-contained, self-priming, self-powered and amenable to low cost manufacture. Formulation chamber 110 is lightweight and disposable and it comprises a wall 111 that surrounds and defines an internal lumen or space 112. Formulation chamber 110 has an inlet 113 for receiving secondary path 102 and it

has an outlet 114 also adapted for placing chamber 110 in secondary path 102. Chamber 110 is made of glass, plastic or the like, and as illustrated it is made of a transparent material for viewing its structure. Chamber 110 can house a beneficial agent or an agent delivery device. An agent formulation formed in chamber 110 leaves chamber 110 through secondary path 102, joins fluid from path 99 at couple 104 and then into common path 103 for infusion into a recipient.

Figure 6 illustrates another parenteral system 10 provided by the invention. System 10 comprises a primary path 118 and a secondary path 119 supported agent fluid delivery position above a patient by looped support 120. Primary path 118 comprises in combination a container 121 that is a reservoir of a pharmaceutically acceptable liquid 122 and it has an internal venting tube 123 which allows air to enter container 121 as medical fluid leaves container 121 and is infused into a patient. Container 121 is a large volume parenteral of a sterile fluid intended for the modification and maintainment of physiological functions in a recipient. Container 121 is closed with a stopper 124 held in place by a crimped rim 125. Venting tube 123 extends through stopper 124 for admitting air into container 121. Container 121 is in fluid communication with drip chamber 126 through its hollow spiked end 127 that pierces stopper 124. Drip chamber 126, is as previously described, used for visibly counting the number of drops 128 of medical fluid 122 that passes through said drip chamber 126 over unit time. Drip chamber 126 comprises an enclosed space for holding medical fluid and it is closed at its end by a pair of caps 129 and 130 that snugly slide over tubular wall 131 to form said sterile fluid chamber. The fluid chamber is made of see-through material such as glass or clear plastic for seeing the drops. Medical fluid 122 leaves drip chamber 126 through a first section of tube 132 that carries medical fluid to formulation chamber 133. Formulation chamber 133 comprises a wall 134 that surrounds an internal space 135 and it is closed at its ends 136 and 137 by closures that fit over said chamber wall. Tube 132 enters closure 136 for establishing fluid communication between the formulation chamber and the drip chamber, and a second tube 138 that passes through a flow regulator clamp 139 transport fluid to a two-way valve 140. Fluid passes through valve 140 into common tube 141 and needle assembly 142 to a recipient.

Secondary path 119 consists of container 143 that is a means for storing a pharmaceutically acceptable liquid 144. Container 143 has an internal venting tube 145 for letting air enter container 143. Container 143 is closed by stopper 146 held in place by rim 147. Container 142 is a minicontainer, or a minibottle and it holds about 100 to 500 milliliters of liquid that is used for continuous drug transport, or for intermittent drug transport to a patient. Container 143 is connected to drip chamber 148 through hollow spike adaptor 149 for sending medical liquid from container 143 through the secondary path to a patient. Drip chamber 148 is designed for counting the number of drop 150 that pass through said drip chamber 148 over time. Medical fluid leaves the drip chamber through a first section of tubing 151 that leads to a formulation chamber 152. Agent formulation chamber 152 is as described earlier comprised of a wall formed of a fluid impermeable material that surrounds an internal space for housing a dosage unit amount of a beneficial agent, or a delivery device. Chamber 152 has a known volume and preferably a volumetric scale thereon for indicating the volume of fluid in said chamber. Chamber 152 has an end 153 adapted for receiving incoming tube 151 and an end 154 adapted for receiving outgoing tube 155. Tube 155 passes through clamp 156 and it can be used as an on-off, or a volume flow regulator for controlling fluid flow rate through the secondary path. Tube 155 conveys fluid carrying beneficial agent from chamber 153 to valve 140, and thence through fluid communicating common tube 141 to needle assembly 142 and into a living recipient.

In operation, parenteral delivery system 10 of Figure 6 is used like parenteral delivery system 10 of Figure 5. That is, system 10 of Figure 6 can be used (1) for administering a preselected medical fluid containing a preselected beneficial agent by opening regulator clamp 139 closing regulator clamp 156 and positioning valve 140 to let fluid flow from tube 138 into tube 149; (2) for administering a different preselected medical fluid containing a different preselected beneficial agent by opening regulator clamp 156 closing regulator clamp 139 and positioning valve 140 to let fluid flow from tube 155 into tube 141 and (3) for administering at a selected dosing time a given volume of fluid containing a known amount of agent by (a) permitting fluid to flow through the primary or the secondary path while setting valve 141 in closed position for the primary or the secondary path, (b) permitting a known volume of fluid to enter either formulation chamber, which volume is ascertained by reading the meniscus against the volumetric scale on the chamber, (c) formulating the agent formulation in the chamber by dissolving a given amount of agent present in the chamber, or delivered by a device therein, in the known volume of fluid, which amount of agent solubility in the fluid dissolves over time, and (d) dosing a recipient with the agent solution whenever desired by positioning valve 141 to let it flow from the desired formulation chamber. Thus, the invention provides for delivering the same fluid and different drugs, or different fluids and different drugs to a patient by preselecting the fluid and the drug for the primary or secondary path. The invention also provides for continuous, alternating or interrupted modes of drug therapy.

Figure 7 represents a parenteral system 10 provided by the invention. Parenteral system 10 is a gravitational flow system for the administration of two medical fluids and two beneficial agents at independent, or cooperating flow rates through two distinct delivery paths, a primary path and a

secondary path. The primary path 158 comprises a container 159 that contains a primary medical liquid 160 to be administered to a patient over a prolonged time and it is supported in delivery position by a hanger 161. Primary fluid supply container 159 is made from glass or transparent non-toxic plastic and it is sealed under sterile conditions. Container 159 is sealed with a rubber stopper 162 held in container 159 by annular retaining rim closure 163.

Primary container 159 is in fluid communication with a drip chamber 164. Drip chamber 164 is in fluid communication with container 150 through a hollow puncture spike 165 that passes through stopper 162 into container 159. Drip chamber 164 is a conventional, vented-type 165 drip chamber well-known to medical practice. Basically, drip chamber 164 is formed of two parts, a conical housing 166 for receiving fluid, and it is capped 167 at its inlet and terminates in an outlet orifice 168. Drip chamber 164 lets air enter the parenteral system through air inlet 161 integrally formed as part of capped inlet 161. Th drip 169 rate of fluid flow from container 159 is regulated by a clamp 170 provided down stream on the primary path. A first section of medical grade tubing 171 inserted into outlet 168 establishes fluid communication between drip chamber 164 and inlet 171 of formulation chamber 172.

Agent formulation chamber 172 is sized and adapted for use in parenteral delivery system 10. Agent formulation chamber 172 is self-contained, self-primary, self-powered and amenable to low cost manufacture. The formulation chamber is light-weight, disposable, and it is made in a presently preferred embodiment of a clear, transparent material such as glass or plastic. Formulation chamber 172 comprises a wall 173 that surrounds and forms an internal space 174, and it has an inlet closure 175 that receives tube 171, and an outlet closure 176 adapted to receive tube 177. Tube 177 passes through clamp 170 designed for restricting the internal diameter of tube 177 for regulating, or stopping the flow of fluid through the primary path. Tube 177 enters a coupler 178 made as a Y-type connecting tube for receiving primary path tube 177 and a common tube 179 that leads to an injection member 180 for administering agent formulation to a patient.

Secondary path 181 comprises a container 182 that is a minicontainer or a minibottle formed of glass or plastic, suitably sealed with a rubber stopper 183 held in container 182 by closure rim 184. Container 182 is supported in delivery position by support 161 and it contains a medical fluid 185 acceptable for both parenteral including intravenous administration and as a transporting carrier for a beneficial agent. Air enters container 182 through an air inlet 186 formed integral as part of spike 187, which spike is hollow and pierces the rubber closure 183 of container 182. The other point 188 of spike 187 passes through the closure inlet 189 of drip chamber 190 for conveying medical fluid drop-like 191 from the container into the drip chamber. Drip chamber 190 is in fluid communication via a tube 192 with formulation chamber 193. Agent formulation chamber 192 is constructed like formulation chamber 172 described in the primary path, and that description is included and is applicable for chamber 193. Formulation chamber 193 is connected to a secondary tube 194, formed of a medically acceptable material, that passes through a V-clamp 195 for regulating or stopping agent formation flow through the secondary path. Tube 194 enters couple 178 for flow into common path 179 for infusion through needle assembly 180 into a patient.

The agent in formulation chambers 172 and 193 can be in any pharmaceutical state, present as agent per se, or in a device, which device forms a fluid formulation comprising an agent and a medical fluid that enters chambers 172 and 193, and a medical fluid that enters chambers 172 and 193, and does not require any reconstitution or admixture prior to use. The flow of medical fluid into formulation chamber 172 or 193 can be started, stopped, regulated, or interrupted by clamp 170, or 195, alone or together, that permits tube 177 or 194 to remain open, shut, or to partially obstruct the passage If fluid through tube 177 or 194, and correspondingly the flow of agent solution likewise can be governed from chamber 172 or193.

In operation, parenteral delivery system 10 as illustrated in Figure 7 can be used by a physician, a nurse, or a practitioner in a hospital setting as follows: (1) for administering medical fluid containing a beneficial agent through the primary path by adjusting regulator clamp 170 to open and by closing regulator clamp 194 to prevent the flow of fluid in the secondary, thus assuring the flow through the primary path and into skin piercing needle 180, (2) for administering a medical fluid containing a beneficial agent through the secondary path by adjusting regulator clamp 195 to open and by closing regulator clamp 170 to prevent the flow of fluid in the primary path, thus assuring the flow through the secondary path and into skin piercing needle 180; and (3) for administering an amount of agent in a known volume of fluid from both paths by regulating fluid flow through regulator clamps 170 and 195, which fluid in both instances mixes into a common fluid at coupling 178 for its subsequent administration to a patient. The operations provided by these embodiments of the invention make available continuous and interrupted administration of two different agents in two different fluids through two different paths, and administration of two different agents in different fluids during the same time interval of agents administration.

Figures 8 through 25 depict structural embodiments of formulation chambers that can be used in the intravenous delivery system of Figures 1 to 7. Figure 8 illustrates a formulation chamber 197 that is light weight, disposable and indicated for use in patients requiring parenteral

administration of a fluid containing a beneficial agent. In Figure 8, chamber 197 comprises a body 198 of tube shape and it has a pair of caps 199 and 200 for forming a closed chamber for containing fluid and agent. Caps 199 and 200 fit body 198 and they are preferably made of self-sealing rubber through which a needle or hollow spike can be inserted, or of rubber with a pre-drilled hole covered by a latex disc through which communication can be made with the inside chamber 197. Formulation chamber 197 can preferably be hermetically sealed, is moisture proof, microorganism impermeable, ionizing ray permeable for sterilizing it.

Figure 9 illustrates a formulation chamber 201 with a section removed for depicting the inside of the hollow body of the chamber. In Figure 9, chamber 201 comprises a wall 202 with a section removed and ends 203 and 204. Closure ends 203 and 204 fit over the body of formulation chamber 201 which ends 203 and 204 are made with a receiving hollow member 205 and 206 for accepting a tube that can slide into or slide over the receiving member. Formulation chamber 201 contains a beneficial agent 207 that is soluble in parenteral fluid, such as in an intravenously acceptable fluid and a film 208 formed of a material for controlling the flow of fluid and agent from chamber 201. Film 208 in a preferred embodiment is formed of an agent release rate controlling polymer, such as a microporous polymer like a polycarbonate, a semipermeable polymer like cellulose acetate, or a diffusional polymer like ethylene-vinyl acetate copolymer. The polymeric film according to the mode of the invention is used in a presently preferred embodiment for governing the rate of release of solution containing agent from chamber 201, that is, agent release and fluid flow through chamber 201. Chamber 201 is illustrated with a film at its exit, and optionally it can have a film at its inlet.

Figure 10 illustrates a formulation chamber 209, in opened view, comprising agent 210 in particle form, a release rate controlling polymer film 211 such as cellulose acetate or the like, and a filter 212. Filter 212 is a conventional filter with a pore size of 0.1 micron to 5 micron, and more preferably 0.22 micron or 0.45 micron, for removing bacteria and unwanted matter from the flowing solution thereby, aiding in maintaining a sterile solution.

Figure 11 illustrates formulation chamber 213 comprises a walled body 214 of tube shape and it has a pair of caps 215 and 216 for forming a closed chamber containing fluid and a delivery system. Caps 215 and 216 fit chamber 213 and they can have an integrally formed tubular extension 217 and 218 for receiving an incoming tube. Hollow tubular member 217 and 218 are preferably round for receiving a tube that slides into, or slides over the member. The delivery system depicted in formulation chamber 213 comprises a multiplicity of tiny timed pills 219 for the controlled delivery of an agent, including drug, into a fluid entering chamber 213. The tiny pills are seen in detail, in opened section pills 220, and they comprise a core of drug 221 surrounded by a wall 222 formed of a release rate controlling material. The tiny timed pills 219 provide a high membrane surface area for achieving high release rates of agent for forming an agent solution. The total number of tiny pills 219 in formulation chamber 213 can be varied as an added means for regulating the amount of agent made available for forming an agent solution. The materials forming wall 222 can be selected from materials that release drug 221 by different physical-chemical mechanisms. These mechanisms include erosion, diffusion and osmosis mechanisms. Wall 222 when releasing drug by osmosis, released drug by bursting. Drug 221 in this embodiment is present in the form of an osmotic solute, such as a therapeutically acceptable salt, and it exhibits an osmotic pressure gradient across wall 222 against an external fluid. The membrane materials used to form wall 222 are those permeable to the passage of an external fluid and substantially impermeable to the passage of drug. Typical materials include a member selected from the group consisting of cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose triacetate, and the like. The osmotic wall can be coated around the drug in varying thickness by pan coating, spray-pan coating, Wurster fluid air-suspension coating and the like. The wall is formed using organic solvents, including methylene chloride-methanol, methylene chloride-acetone, methanol-acetone, ethylene dichloride-acetone, and the like. Osmotic wall forming materials, procedures for forming the wall, and osmotic bursting procedures are disclosed in United States Pt. Nos. 2,799,241; 3,952,741; 4,014,334; and 4,016,880.

Wall 222 of tiny pills 213 in another embodiment can be made of a drug release rate controlling material. That is, drug 221 dissolves in the wall or through pores within the wall and passes through the wall or through said pores at a controlled rate by diffusion over time. Exemplary materials useful for forming a diffusional wall or a wall with pores include ethylene-vinyl acetate copolymer, ethyl cellulose, polyethylene, cross-linked polyvinyl pyrrolidone, vinylidene chloride-acrylonitrile copolymer, polypropylene, silicone, and the like. The wall can be applied by techniques described above, and materials suitable for forming wall 81 are described in United States Patent Nos. 3,938,515; e,948,262; and 4,014,335.

Wall 222 of tiny pills 213 can be made of bioerodible material that bioerodes at a controlled rate and releases drug 221 to the fluid in chamber 213. Bioerodible materials useful for forming wall 222 include a polycarboxylic acid, polyesters, polyamides, polyimides, polylactic acid, polyglycolic acid, polyorthoesters, and polycarbonates. These polymers and procedures for forming wall 222 are disclosed in United States Pat. Nos. 3,811,444; 3,867,519; 3,888,975; 3,971,367; 3,993,057; and

4,138,344. The amount of drug present in a tiny timed pill generally is about 10 ng. to 20 mg, and the number of tiny pills in a chamber is about 10 to 1000, preferably 50 to 150. The tiny pills comprising the wall and the inner core of drug have a diameter of at least 100 microns, and in a presently preferred embodiment a diameter of at least 2000 microns. The tiny pills can have one or more coatings of wall-forming materials thereon. Chamber 213 optionally is equipped with a support 223 for the tiny pills. Support 223 can be a film having release rate controlling properties and made of a polymer that releases drug from chamber 213, support 223 can be a microporous polymeric membrane, a sintered glass support, a perforated grid, and/or the like.

Figure 12 illustrates a formulation chamber 224 illustrating a similar chamber comprising a wall 226 surrounding a lumen 227 having an inlet 228 and an outlet 229. Chamber 224 houses a plurality of tiny capsules 230 further seen in opened section capsule 231. Capsules 230 comprise a wall 232 surrounding a mass of liquid drug 233. The tiny capsules can be made by coacervation technique consisting essentially of forming three immiscible phases, a liquid manufacturing phase, a core material phase and a coating phase. The coating phase is deposited as a liquid on the core material and rigidized usually by thermal, cross-linking or desolvation techniques, to form tiny microcapsules. The capsules made by this technique have an average particle size of from several tenths of a micron to 5,000 microns, and in some embodiments a larger tiny capsule can be used herein. Particle size however, is not critical in the practice of this invention. Suitable techniques for preparing tiny microcapsules are reported by Bungenberg de Jong and Kass, *Biochem. Z.*, Vol. 232, pages 338 to 345, 1931; *Colloid Science*, Vol. 11, "Reversible System," edited by H. R. Kruyt, 1949, Elsevier Publishing Co., Inc., New York; *J. Pharm. Sci.*, Vol. 59, No. 10, pages 1,367 to 1,376, 1970; and *Pharmaceutical Science*. Remington, Vol. XIV, pages 1,676 to 1,677, 1970, Mack Publishing Co., Easton, PA. Formulation chamber 224 also contains a film 234 that supports the tiny capsules and which film can also serve as a means for regulating the release of drug solution from formulation chamber 224.

Figure 13 illustrates a formulation chamber 236 comprising a wall 237 that surrounds an internal lumen 238 with an inlet end 239 and an outlet end 240. Chamber 236 houses a multiplicity of hollow fibers 241, with one fiber seen in opened section comprising a wall 242, that can be formed of a semipermeable polymer, a diffusional polymer, a microporous polymer, a lamina, or a laminate or two or more lamina, surrounding a lumen 243 containing drug 244. The hollow fibers provide a large exposed surface area for concomitantly releasing a large amount of agent into the formulation chamber. The hollow fibers can have a length of a few millimeters to many centimeters or longer, a diameter of a millimeter or larger, and the chamber houses at least one hollow fibre to several hundred or more. The hollow fibers have openings at each end 241a, 241b, and they can be produced from non-cellulosic polymers using melt spinning techniques using shaped spinnerettes. Hollow fibers can also be produced by spinning an organic solvent cellulosic solution into certain regenerants, n-octanol where the solvent is dialkylacylamide, and n-hexanol where the solvent is dimethylsulfoxide. The hollow fibers can be filled with drug by using a solution of drug injected into one opened end of the fiber, by soaking in a drug solution, and the like. The hollow fibers can release an agent by diffusion, dialysis, osmotic, leaching and like techniques. The amount of agent released from the fibres further can be regulated by selecting the dimension and number of hollow fibers housed in the formulation chamber. A procedure for manufacturing hollow fibers is disclosed in U.S. Pat. No. 4,086,418. Formulation chamber 236 optionally contains a support 245 for holding the fiber which support permits the passage of drug formulation from chamber 236.

Figure 14 illustrates a formulation chamber 246, seen in opened section, and it comprises a wall 247 that surrounds a lumen 248 with an inlet 249 and an outlet 250 for admitting and exiting fluid from chamber 246. Chamber 246 houses a multiplicity of fibers 251 containing drug 252, represented by dots. The fibers 251 forming the drug delivery system can be of natural or synthetic origin, and they can have a wide variety of structures, such as solid, semi-solid, porous, and the like, a variety of geometric shapes such as round, oval, square, trilobal, various lengths and cross-sections, and the like. The fibers can function effectively as a reservoir by having drug dispersed therethrough. Suitable fibers can be made by conventional fabrication techniques. For example, fiber material and drug may be dissolved in a solvent, extruded through small holes of a die and then solidified by standard melt spinning, wet spinning, or dry spinning techniques. In another embodiment, the fibers can be produced by pumping a melt of fiber and drug through a spinneret. With such a method, fiber diameter may be varied from a few tenths to a micron to a millimeter or so by down-drawing, or by up-drawing techniques. The lumen of the chamber can house fibers of mixed denier. The fibers forming the reservoir can be filled, saturated, or semi-filled with drug by immersing, soaking or the like and permitting the desired amount of drug to transfer into the fibers. Other techniques and drugs for forming fibers are disclosed in U.S. Pat. Nos. 3,228,997 and 3,921,636. The materials forming the fibers can be polyolefins, polyamides, polyurethanes, cellulosic materials and the like. Fiber procedures are set forth in *Encyclopedia of Science and Technology*, Vol. 5, pages 263 to 276, 1971, published by McGraw Hill Co., New York. Chamber 246 also contains a membrane 253 for supporting the fibers and it can be formed of a diffusional or porous polymer for cooperating

with the fibers for regulating the amount of drug solution infused into a patient.

Figure 15 illustrates a formulation chamber 255 having a section of its wall 256 removed for depicting the internal space 257 as a means for housing a beneficial agent delivery system 258. System 258 comprises a reservoir formed of an erodible polymer, and a section is removed 259 for illustrating agent 260 dispersed therein. The erodible polymer can be a member selected from the group including polyorthoesters, polyorthocarbonates, polyglicolic acid, polylactic acid, polyacetals, polyketals, polyamino acids, and the like. Procedures and erodible polymers are disclosed in United States Pat. No. 4,180,646; in *Int. J. of Pharmaceutics,* Vol. 7, pages 1 to 18, 1980; in *Biodegradables and Delivery Systems for Contraception,* Chapter 2, edited by E. S. E. Hafex and W. A. A. Van Os, published by G. K. Hall, Boston, 1980. Chamber 255 can also have a release rate controlling polymeric film 261 such as cellulose acetate or the like, and a filter 262. Filter 262 is a conventional filter with a pore 263 having pore size of 0.1 micron to 5 micron, and more preferably 0.11 micron or 0.45 micron, for removing bacterial and unwanted matter for flowing solution, thereby aiding in maintaining a sterile solution.

Figure 16 illustrates a formulation chamber 265 housing an agent delivery system comprising a plurality of ion-exchange resin particles 266 having an agent 267 ionically attracted thereto. The resins can be particles, bead, and droplet shaped. The particles and the like can vary in size, usually from 10 to 350 mesh. The resins can be homopolymers, copolymers, derivatives thereof, or cross-linked resins. Typical resins include ion-exchange resins such as cross-linked styrene-divinyl benzene and the like, having agent 267 ionically bonded thereto. Active agent 267 is released from resin 266 into fluid that enters the formulation chamber to form in the chamber an agent solution for administering to a patient. Chamber 265 also can house a release rate controlling film 268 and a filter 269 having pores 270 for preventing bacteria and unwanted matter from leaving the formulation chamber. The ion-exchange resins are disclosed in United States Patent No. 4,203,440.

Figure 17 depicts a formulation chamber housing a delivery device. The formation chamber can be used in a primary path, a secondary path, or in both paths, that is, the formulation chambers illustrated herein can be used in either or both paths. Agent formulation chamber 272, as seen in Figure 17 is another unique component of the parenteral delivery system. Formulation chamber 272 is the unique component of the parenteral delivery system, and in the embodiment illustrated, the formulation chamber comprises a wall 273 that surrounds and defines an internal space 274. Chamber 272 has an inlet 275 adapted and sized for placing chamber 272 into an intravenous delivery system, and it has an outlet 276 also adapted and sized for placing the chamber in the system. Inlet 275 and outlet 276 are made for receiving an incoming or outgoing tube. Chamber 272 is manufactured of glass, plastic or the like, and as illustrated it is made of a transparent material for illustrating its structure and a device housed therein. In the embodiment shown, chamber 272 comprises a pair of interfitting housing halves 277 and 278 for containing agent delivery device 279 within space or lumen 274. A retaining means 280 in housing 278 permits the passage of fluid, keeps device 279 in lumen 274, and it also prevents device 279 from blocking outlet 276.

The delivery device 279 illustrated in Figure 17 an osmotic rate-controlled solid dosage delivery form as described by patentee Felix Theeuwes and Takeru Higuchi in United States Patent No. 3,845,770. The osmotic device 279 seen in transparency comprises a semipermeable wall 281, such as cellulose acylate, cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, and the like, that surrounds and forms a compartment 282 containing an agent 283, or drug represented by dots. The agent formulation 283 exhibits an osmotic pressure gradient across wall 281 of device 279 against fluid in chamber 272. The agent formulation can comprise an agent that exhibits an osmotic pressure gradient, or the agent formulation can comprise an agent mixed with an osmotically effective solute, such as sodium chloride, potassium chloride, and the like that exhibit an osmotic pressure gradient substantially greater than the fluid in chamber 272. A passageway 284 extends through semipermeable wall 281 and communicates with compartment 282 and the exterior of device 279. In operation fluid enters chamber 272 and is imbibed through the semipermeable wall 281 of device 279 into compartment 282 in a tendency towards osmotic equilibrium at a rate determined by the permeability of the wall and the osmotic pressure gradient across the wall, thereby producing a solution containing agent 283 in compartment 282 that is dispensed through passageway 284 at a rate controlled by device 279 over a prolonged period of time. The delivery of agent solution from device 279 for homogenously blending with fluid in chamber 272 is controlled in this embodiment by device 279 and it is essentially independent of the rate of fluid flow through chamber 272. Device 279 maintains its physical and chemical integrity throughout its releasing history.

Figure 18 depicts agent formulation chamber 272 in opened section, containing another device 285 for delivering an agent into an intravenously acceptable fluid that enters chamber 272. Device 285 is illustrated in opened-section and it comprises an inner mass transfer conductor 286, illustrated as a solid core and formed of a polymeric material such as cured polydimethylisoxane, with agent 287 dispersed therethrough. Surrounding mass transfer conductor 286 is an agent release rate controlling membrane 288 preferably formed of a polymeric

material, such as polyethylene. Both conductor 286 and membrane 288 are permeable to the passage of agent 287 by diffusion, that is, agent can dissolve in and diffuse through conductor 286 and membrane 288. However, the permeability of conductor 286 is greater than that of membrane 288, and membrane 288 thus acts as the rate controlling member for agent release from device 285. Device 295 maintains its physical and chemical integrity throughout the period of agent delivery. Agent delivery device 285 is disclosed in United States Pat. No. 3,845,480.

Figure 19 illustrates the agent formulation chamber, with a section of its wall removed, housing delivery device 289 for delivering an agent at a rate controlled by device 289 into a fluid that enters chamber 272. Device 289 is seen in opened-section and it comprises a reservoir 290 formed of a liquid mass transfer conductor 291 such as a medical oil liquid carrier, permeable to the passage of agent, containing agent 292 such as the drug phenobarbital. Reservoir 290 is surrounded by a wall 293 formed of an agent or drug release rate controlling material permeable to the passage of agent 292, such as polyolefin. The rate of passage of agent 292 is lower through wall 293 than the rate of passage through conductor 291, so that agent release by wall 293 is the agent release rate controlling step for releasing agent 292 from device 289. Device 289 maintains its physical and chemical integrity throughout its agent release history. Agent delivery device 289 is disclosed in United States Pat. No. 3,993,073, which patent is incorporated herein.

Figure 20 illustrates agent formulation chamber 272, with a part of its wall removed, housing another device 294 for delivering an agent into a liquid that enters a chamber 272 for forming an intravenously acceptable agent formulation. Device 294 is seen in opened-section and it comprises a wall 295 surrounding a reservoir 296 containing agent 297. The reservoir is formed of a solid carrier permeable to the passage of agent such as cured polydimethylsiloxane containing the drug diazepam. Wall 295 is formed of a microporous material, the pores of which contain an agent release rate controlling medium permeable to the passage of agent 297 for example, formed of a microporous polymer made by coprecipitation of a polycation and a polyanion. The release of agent 296 is controlled by device 294, which device maintains its physical and chemical integrity during the period of time it is in chamber 272. Device 294 is disclosed in United States Pat. No. 3,993,072, which patent is incorporated herein by reference.

Figure 21 is a view of formulation chamber 272 having part of its housing removed and housing device 298 for delivering an agent into a medical fluid that enters chambers 272 for forming in situ an intravenously acceptable agent formulation solution. Device 298 comprises a matrix 299 containing agent 300 distributed therethrough. Matrix 299 is formed from a polymeric material that is non-erodible, that is, it keeps its physical and chemical integrity over time, and it is permeable to the passage of agent 300 by the process of diffusion. The rate of agent release from the matrix is determined by the rate the agent dissolves in and passes through the matrix by diffusion, so that from the matrix it is the agent release rate controlling step. The matrix can possess any shape such as rod, disc and the like that fits into chamber 272. The polymers include polyolefins such as polyethylene containing muscle relaxants and the like. Materials useful for manufacturing the devices are disclosed in United States Pat. No. 3,921,636.

Figure 22 is a view of agent formulation chamber 272, in opened view, housing device 301 for delivering an agent into a fluid that enters chamber 272. Device 301 is seen in opened section, and it is formed of a microporous polymeric material 302 containing agent 303 distributed therethrough. Matrix 302 is formed of a non-toxic, inert polymer, that is non-erodible and has a plurality of micropores for releasing agent at a controlled rate to fluid entering chamber 272. Microporous materials useful for the present purpose are disclosed in United States Pat. Nos. 3,797,494 and 3,948,254.

Figure 23 illustrates agent formulation chamber 272, in opened view, housing device 304 for delivering an agent into a medical fluid that enters chamber 272. Device 304 is seen in opened section and it comprises depots of agent solute 305 dispersed in and surrounded substantially individually by a polymer 306 that is impermeable to the passage of agent solute and permeable to the passage of fluid that enters chamber 272. Agent or a medication solute 305 exhibits an osmotic pressure gradient across the polymer against fluid that enters chamber 272. Agent 305 is released at a controlled rate by fluid from the chamber being imbibed through the polymer into the depots to dissolve the solute and generate a hydrostatic pressure in the depots, which pressure is applied against the wall of the depots thereby forming apertures that release the agent at a controlled rate over time. Polymer 306 is non-erodible, and device 304 can be shaped as a matrix, a rod, a disc, or like shapes. Procedures and materials useful for manufacturing osmotic bursting delivery systems are described in United States Pat. No. 4,177,256.

Figure 24 illustrates agent formulation chamber 272, in opened view, containing device 307 useful for delivering an agent into a medically acceptable fluid passing through chamber 272. Device 307 is seen in opened view and it comprises an exterior wall 308 formed of a semipermeable polymer permeable to fluid and substantially impermeable to the passage of agents and solutes. A layer 309 of an osmotically effective solute, for example sodium chloride, is deposited on the inner surface of wall 308. Solute layer 309 surrounds an inner container 310 formed of a flexible material that is impermeable to solute and agent. Container 310 has a passageway 311 for delivering an agent 312 into a fluid in chamber 272. Device 307

dispenses agent by fluid permeating from chamber 272 through the outer wall 308 to continuously dissolved solute 309 in a tendency towards osmotic equilibrium, thereby continuously increasing the volume between wall 308 and container 310. This increase causes container 310 to continuously collapse and dispense agent 312 from device 307 at a controll rate through passageway 311 to fluid passing through chamber 272. Osmotically powered agent dispensing devices are disclosed in United States Pat. Nos. 3,760,984 and 3,995,631.

Figure 25 illustrates a formulation chamber 314 made with an internal pocket 315 for containing agent 316, for example a drug such as ephedrine sulfate. Pocket 315 is formed of a wall 317 made of a mterial such as a diffusional, semipermeable, or a microporous polymer that permits the passage of medical fluid into pocket 35 and agent solution formed therein from pocket 315. In an embodiment, when wall 317 is a semipermeable polymer, it can be provided with a delivery orifice to dispense the agent solution into chamber 314. Wall 317 is joined by adhesive, heat sealing or the like to wall 318 of chamber 314. Wall 318 is made of a material substantially impermeable to the passage of agent, medical fluid and agent solution formed therein. In operation, fluid enters chamber 314 and then into pocket 315, wherein it forms a solution containing the agent that passes into chamber 314 and then is administered therefrom to a recipient. The system in Figure 25 allows regulation of fluid flow independently from agent delivery. Delivery is governed by the mass transport characteristics of membrane 317, and fluid flow is governed by a resistance element, for example, a flow regulator, in the fluid path.

The parenteral delivery system can be used for administering many beneficial agents, especially where it is desirable to administer by infusion, and more particularly via the intravenous, intra-arterial, intraperitioneal, or subcutaneous routes. For example, in one embodiment, for intraperitioneal administration of fluid and beneficial drug, the parenteral administration set is connected to a cannula transvering the abdominal wall of the patient. The parenteral delivery system in a presently preferred embodiment is used for intravenous therapy. In intravenous therapy, the parenteral delivery set can be used in intravenous fluid replacement, such as administering plasma, saline, or the like and simultaneously, or intermittently administering a therapeutically effective amount of drug therewith; in another embodiment in a method of intravenous electrolyte-balance replacement, such as supplying sodium, potassium, chloride ions, or the like with a drug administered therewith to a patient in need of electrolyte restoration and intravenous drug; and in a method of intravenous nutrition, such as supplying dextrose and concomitantly administering or periodically administering a parenterally administrable drug to a patient in need of such therapies. Also, the parenteral delivery system comprising the primary path, the secondary path with agent formulation chambers in one, or in both paths, can be used as an intravenous therapy system in the practice of veterinary medicine.

CLAIMS

1. A parenteral delivery system comprising a container for a pharmaceutically acceptable fluid means for introducing fluid from said container to a patient, conduit means connecting said container and said introduction means, said conduit means including a drip chamber for determining the rate of fluid flow within said conduit means, and a formulation chamber disposed to debouch into said conduit means downstream of said drip chamber and adapted to contain a pharmaceutically acceptable formulation capable of forming a fluid agent formulation with said fluid for supply thereof to the patient.

2. A system according to Claim 1, wherein the parenteral delivery system comprises a common path in communication with the drip chamber for receiving fluid from the drip chamber, and in communication with the formulation chamber for receiving a fluid agent formulation from the formulation chamber.

3. A system according to Claim 1 or Claim 2, wherein the formulation chamber in communication with the drip chamber; the formulation chamber comprising:

1) a wall surrounding a lumen;

2) an inlet for admitting a fluid from the drip chamber into the formulation chamber;

3) an outlet for letting fluid leave the formulation chamber; and,

4) a beneficial agent in the formulation chamber for forming a fluid agent formulation with fluid admitted into the formulation chamber.

4. A system as claimed in any one of the preceding claims wherein the formulation chamber is disposed in the conduit means downstream of the drip chamber.

5. A system according to any preceding claim, wherein the formulation in the formulation chamber is present in an agent delivery device.

6. A system according to any preceding claim, wherein the formulation in the formulation chamber is present in unit dosage form.

7. A system according to any preceding claim, wherein the formulation is a drug.

8. A system according to any preceding claim, wherein a membrane is present in the formulation chamber for aiding in controlling the rate of release of formulation agent in the formulation chamber.

9. A system according to any preceding claim,

wherein conduit means comprises a tube for conveying fluid from the formulation chamber.

10. A parenteral delivery system as claimed in Claim 1 and substantially as herein described with reference to and/or as illustrated in the accompanying drawings.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1983. Published by the Patent Office 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.